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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/699,338	10/31/2003	Birgit Sehested Hansen	6443.500-US	2536

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EXAMINER	
KWON, BRIAN YONG S	

ART UNIT	PAPER NUMBER
1614	

NOTIFICATION DATE	DELIVERY MODE
03/20/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/699,338	HANSEN ET AL.	
	Examiner	Art Unit	
	Brian-Yong S. Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,5-9,14,15 and 17* is/are pending in the application.

4a) Of the above claim(s) *8 and 9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,5-7,14,15 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. Acknowledgement is made of applicants' filing of the instant application as a Request for Continued Examination (RCE) under 37 CFR 1.1114.

2. Acknowledgement is made of applicant's filing of amendment/remarks on 12/21/2007. By the amendment, claims 2 and 17 have been amended and claims 1, 12, 13, 20 and 44-49 have been cancelled.

3. The rejection of claims 2, 5-7 and 14-15 under 35 USC 112, 1st paragraph, as containing subject matter which was not described in the specification is not maintained in light of the amendment filed 12/21/2007.

4. The rejection of claims 2, 5-7, 14-15 and 17 under 35 USC 112, first paragraph, as lacking enablement for treating various diseases conditions encompassed by the instant claims with the administration of compound of formula I is not maintained in light of the amendment filed 12/21/2007. However, the amendment changing the scope of the invention by reciting "endometrial cancer, breast cancer, prostate cancer and colon cancer" and formula III compounds in claim 2 necessitates a new ground of rejection in this Office Action.

5. The rejection of claims 2, 5-7, 14-15 and 17 under 35 USC 103(a) is maintained for the reasons of record. No arguments to the examiner's contentions have been present by applicant in Response filed 12/21/2007. In absence of applicant's argument explaining how the claims avoid the references or distinguish from them, the examiner maintains the rejection of record.

6. As discussed above, rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or

newly applied. They constitute the complete set of actions being applied to the instant application.

7. Claims 2, 5-7, 14-15 and 17 are currently pending for prosecution on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 2, 14-15 and 17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for method of increasing glucose utilization, treating diabetes or obesity and/or impaired glucose tolerance with the administration of the specific compound of the formula III, does not reasonably provide enablement for treating atherosclerosis, hypertension, dyslipidemia, coronary heart disease, gallbladder disease, osteoarthritis, endometrial cancer, breast cancer, prostate cancer and colon cancer with all compounds encompassed by the instant invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are'. (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of

the art; (5) the breadth of the claims; (6) the amount .... of direction or guidance presented; (7) the presence or absence of working examples; and (81) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

The instant invention relates to a method of treating a disease condition benefiting from an enhancement of mitochondrial respiration, namely obesity, atherosclerosis, hypertension, diabetes, type 2 diabetes, impaired glucose tolerance, dyslipidemia, coronary heart disease, gallbladder disease, osteoarthritis and cancer, by the administration of the claimed compound(s) represented by the formula I having a slope calculated from an equation or a pharmaceutically acceptable salt or solvate thereof.

The relative skill of those in the art of pharmaceuticals and the unpredictability of the pharmaceutical art are very high. In fact, the courts have made a distinction between mechanical elements function the same in different circumstances, yielding predictable results, chemical and biological Compounds often react unpredictably under different circumstances. Nationwide Chem. Corp. v. Wright, 458 F. supp. 828, 839, 192 USPQ 95, 105(M.D. Fla. 1976); Affd 584 F.2d 714, 200 USPQ 257 (5th Cir. 1978); In re fischer, 427 F.2d 833, 839, 166 USPQ 10, 24(CCPA 1970). Thus, the physiological activity of a biological compound is considered to be an unpredictable art and the physiological or pharmaceutical activity of treating "a disease condition benefiting from an enhancement of mitochondrial respiration..." is an unpredictable art.

The claims are very broad due to the vast number of possible diseases conditions that are described as being "a disease condition benefiting from an enhancement of mitochondrial

respiration" including "obesity, atherosclerosis, hypertension, diabetes, type 2 diabetes, impaired glucose tolerance, dyslipidemia, coronary heart disease, gallbladder disease, osteoarthritis, cancer, endometrial cancer, breast cancer, prostate cancer, colon cancer and the maintenance of a weight loss". Furthermore, the claims are further complicated by plethora of compounds having characteristic of "a slope value calculated from the equation", particularly compounds of the formula (III).

At the time of the invention was made, it was generally recognized in diabetes therapy art that the intensive blood-glucose control with anti-diabetic substantially decrease the risk of microvasuclar complications, such as retinopathy, neuropathy and nephropathy, but not macrovascular disease such as hypertension, atherosclerosis and cardiovascular outcomes (see Lancet, Vol. 352, Sept. 12, 1998).

Although some known chemical uncouplers that have activities in increasing the metabolic rate may be useful in treating obesity or diabetes, it is not known yet that a single underlying mechanism ties together all of the seemingly unrelated manifestation of the disease conditions encompassed (for example, atherosclerosis, hypertension, dyslipidemia, coronary heart disease, gallbladder disease, osteoarthritis, endometrial cancer, breast cancer, prostate cancer and colon cancer). There is no demonstrated correlation or sufficient evidence in the specification or incorporated by reference that increased glucose utilization would be able to treat all the diseases encompassed by the instant claims. Therefore, the skilled artisan would turn to undue amount of trial and error to find out which disease or condition would be response to the administration of sad compounds.

The specification discloses the effects of increased glucose utilization (Figures 1- 3) using the compounds that have a slope value calculated from an equation. However, the specification fails to provide how to use the invention commensurate in scope with these claims without undue amount of experimentation. As discussed in preceding comments, in the instant case, only a limited number of "a compound capable of increase glucose utilization" in vitro study is disclosed in the specification, thereby the specification fails to provide sufficient working examples. It is noted that these examples are neither exhaustive, nor define the class of compounds required. The instant claims read on any compounds of formula III having "a slope value calculated from the equation", necessitating an exhaustive search for the embodiments suitable to practice the claimed invention. Applicants fail to provide information sufficient to practice the claimed invention, absent undue experimentation.

As discussed in preceding comments, to practice the instant invention to the claimed scope, applicant would have to (i) make or screen numerous potentially suitable compounds of the formula I characterized as "having a slope value calculated from the equation", (ii) undergo assays to find out which compounds are able to exert the desired pharmacological activity, and then (iii) extrapolate the test and result to the claimed therapeutic utility. In other words, the instant invention necessitates for the skilled artisan to undergo an exhaustive search for the embodiments suitable to practice the claimed invention.

Given the breadth, the disparate nature of compounds that is presently claimed, the highly unpredictable state of the art where many specific differences or different physicochemical properties are existed among unrelated structural compounds or even structurally related compounds, the limited number of working examples and the insufficient amount of guidance

present in the specification, one of ordinary skill in the art would have to undergo an undue amount of experimentation to practice the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 2, 14-15 and 17 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 2 recites the broad recitation "diabetes", and the claim also recites "type 2 diabetes" which is the narrower statement of the range/limitation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 2, 14 and 15 are rejected under 35 U.S.C. 102(b) as being anticiapted by Tang et al. (US 5891917).

Tang discloses (E)-2-benzenesulfonyl-3-(3,5-di-tert-butyl-4-hydroxy-phenyl)acrylonitrile and (E)-3-(3,5-di-tert-butyl-4-hydroxy-phenyl)-2-(4-fluoro-benesulfonyl)-acrylonitrile which reads on the instant formula III compounds, as tyrosine kinase inhibitors, that is useful for the treatment of diseases mediated through HER2, EGFR, IGFR, KDR/FLK-1 and C-MET disorders including breast cancer, endometrial cancer, colorectal cancer, non-small cell lung cancer, gastric, ovarian adenocarcinomas, prostate cancer and diabetes (entire documents, especially columns 3-4; column 8, line 56 through column 9, line 11; column 9, lines 42-48; column 10, line 53 through column 11, line 7; column 10, line 56 through column 12, line 2; Examples 7, 18, 36, 66, 78 and 81).

With respect to the recitation of "increasing mitochondrial respiration" in the claims, when the same compound is administered to treat the same patient population, the mechanism of action of "increasing mitochondrial respiration" deems to be inherent to the referenced method. Therefore, the reference anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

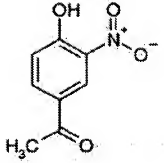
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 2, 5-7, 14-15 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bachynsky (US Patent 4,673,691, issue date: Jun. 16, 1987) in view of Batt et al. (US Patent 5,593,994, issue date: Jan. 14, 1997) and Rink et al. (US Patent 5,739,106, issue date: Apr. 14, 1998) as applied to claims 4-7. This rejection is analogous to the original rejection.

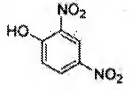
The instant claims are directed to a method comprising the administration of a compound of formula III having a slope calculated from an equation as defined in the claim. Further limitation include that the method is for treating a disorders, such as type II diabetes, obesity, atherosclerosis, hypertension, impaired glucose tolerance, dyslipidemia, coronary heart disease, gall bladder disease, osteoarthritis and endometrial cancer, breast cancer, prostate cancer and colon cancer in a patient.

A compound for the treatment is the elected species of 4-hydroxy-3-nitroacetophenone



having the following structure:

Bachynsky teaches a method of inducing weight loss in a patient comprising administering 2,4-dinitrophenol (DNP) (column 6, lines 20-22) having the following structure:



The prior art teaching differs from the instant invention in that (i) the prior art compound has a nitro group at position 4 whereas the compound of the instant invention has an aceto group at position 4 and (ii) the prior art does not disclose that the obese patient has type II diabetes. However, the base structure of the prior art compound 2,4-dinitrophenol is the same as the base

structure of 4-hydroxy-3-nitroacetophenone of the instant invention and the physiological activities are analogous. In addition, Batt et al. disclose compounds for treatment where the substitute groups on the benzene ring can be nitro or aceto (column 49, line 39). Therefore, the substitution of a nitro group with an aceto group on the benzene ring is obvious. One having ordinary skill in the art would have been motivated to substitute a nitro group of the prior art compound with an aceto group with the expectation that the substitution would not significantly alter the analogous properties of the compound due to close structural similarity of the compounds. See In re Grunwell, 203 USPQ 1055. With respect to the patient population for treatment in claims 4-7 where the patient who is obese is suffering from type II diabetes, Rink et al. disclose that obesity and type 2 diabetes are associated in both clinical and epidemiological studies (column 1, lines 29-31) and that weight reduction is often recommended as the first course of action for patients suffering from Type II diabetes (column 1, lines 42-45). Therefore, one having ordinary skill in the art would have been motivated to practice a weight reduction method of treatment to treat obese patient who is suffering from Type II diabetes.

Therefore, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to practice the treatment of Bachynsky in view of Rink et al. with compound modifications in view of Batt et al. to result in the practice of the instant invention with a reasonable expectation of success.

The recitation of the compound having a slope calculated from an equation as defined in claims 2, 5-9 and 14-17 is merely a characterization of the compound and therefore does not limit the claims.

With respect to the recitation of "increasing mitochondrial respiration" in the claims, when the same compound is administered to treat the same patient population, the mechanism of action of "increasing mitochondrial respiration" is expectedly present.

Regarding the recitation of claim 14, since there is no extra active step in the method of treatment for conducting the Assay, the compound being a chemical uncoupler as defined is merely a characterization of the compound and therefore does not limit the claim.

Regarding the recitation of claim 15, since the nitro group of the prior art compound is the same nitro group of the instant compound, the fact that the nitro group is a cation is merely a characterization of the compound and therefore does not limit the claim.

12. Claims 5-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tang et al. (US 5891917) in view of Tang et al. (US 6514981).

The teaching of Tang'917 has been discussed in above 35 USC 102(b) rejection.

Tang'981 teaches the use of tyrosine kinase inhibitor for the treatment of various disese conditions including obesity (column 40, line 48 and column 51, line 60) and diabetes, particularly type II diabetes (column 51, line 55 and lines 66-67; column 52, line 35).

The teaching of Tang'917 differs from the instant invention in the use of said compounds for the treatment of obese-type II diabetes. To incorporate such teaching into the teaching of Tang'917, would have been obvious in view of Tang'981 who teaches the utility of tyrosine kinase inhibitor in the treatment obesity and type II diabetes.

Thus, one would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients

and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

Conclusion

13. No Claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system, see http://pair-direct.uspto.gov Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

/Brian-Yong S Kwon/
Primary Examiner, Art Unit 1614